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Clinical Immunology 186 (2018) 79–81

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Should radiographic progression still be used as outcome in RA?

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ARTICLE INFO

Article history:
Received 13 July 2017
Accepted with revision 19 July 2017
Available online 22 July 2017

Keywords:
Radiographs
Rheumatoid arthritis
Structural damage
Clinical trials

ABSTRACT

Radiographs of hands and feet are traditionally the images that are used to assess structural damage progression in drug trials in patients with rheumatoid arthritis, aiming at proving the disease modifying capacity of a drug. Although treatment has largely improved over the past decade and consequently radiographic progression is limited in control arms in clinical trials, recent trials are still able to show inhibition of structural progression by new drugs. The requirements for the successful use of radiographic progression as an outcome in rheumatoid arthritis trials will be discussed in this paper.

Drug treatment in RA traditionally distinguishes treatment with symptom modifying and disease modifying antirheumatic drugs (SMARDs and DMARDs). Disease modification is based on the preservation or normalisation of physical function as well as inhibition of structural damage progression. Traditionally, structural damage is assessed on radiographs of hands and feet, measuring both bone resorption as erosions and cartilage degradation as joint space narrowing. Radiographs of hands and feet provide a good representation of the overall damage that may also occur in large joints [1]. Over the years, it has been proven useful to make the distinction between SMARD and DMARDs particularly by assessing damage on radiographs. It has also become clear that progression of damage can be inhibited by many different DMARDs and that in general the biological (b) and targeted synthetic (ts) DMARDs are more efficacious than the conventional synthetic (cs) DMARDs. It has been proven also that inflammation in individual joints results in damage of that particular joint [2]. Moreover, overall disease activity is directly related to functional disability and is leading to structural joint damage [3,4]. In addition, structural damage contributes to functional disability [5]. As structural damage is largely irreversible, physical disability caused by structural damage is irreversible, while the function loss related to disease activity may still be reversible [6]. Drug treatment of RA therefore focuses on reducing inflammation and preventing joint damage, thereby improving function and reducing disability. Structural damage is also related to reduced work participation. In a recent analysis, an increase of 10 points in the baseline damage score was associated with a 9.6% decrease in the odds of achieving a favourable employment status [7].

Initially, the usual duration of trials assessing structural damage was 52 weeks. Later, it became clear that 24 weeks is a sufficient follow-up period and even trials with a follow-up as short as 12 weeks could show progression of structural damage [8]. The progression observed in the control group largely determines the possibility of showing an inhibitory effect by an effective drug. However, it is evident that the level of progression observed in clinical trials has decreased over the years, both in the actively treated and the control groups [9]. Moreover, in the first executed trial in the late nineties the observed yearly progression rate in the control group was similar to the estimated yearly progression rate at baseline. In more recent trials, the observed progression was much lower than the expected progression based on the rate of progression at baseline. One of the explanations is a better overall standard of care. Furthermore, ethical considerations and the availability of effective treatments prohibit duration of placebo treatment sufficiently long to pick up changes. Typically, the placebo period is limited to 12–16 weeks. Moreover, there is a mandatory early escape to switch to an effective treatment in case of clinical inefficacy, and this has an immediate impact on the progression of structural damage.

Data of structural progression are usually presented on a group level as the mean progression, and on a patient level. The mean progression score is a difficult to interpret figure because it is usually based on highly skewed data: while many patients do not show any change, a minority either shows an improvement or a deterioration. The patient-level information is frequently presented as the percentage of patients showing progression above a certain cut-off, but ideally all individual patient data should be presented in a cumulative probability plot, showing the coherence and the number of patients with improvement and deterioration [10]. While the mean progression in the control arms of the

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http://dx.doi.org/10.1016/j.clim.2017.07.022

first trials was approximately 7 units, more recent trials have shown mean progression scores of only 1 unit [9]. This makes people argue if a mean reduction of e.g. 0.5 units is still clinically relevant. The mean progression score is indeed the best primary endpoint to assess the efficacy of a drug in comparison to placebo or another drug, but it should not be used to assess the clinical relevance. The same trial result may also be presented as 'the likelihood of radiographic progression above 5 units per year decreases from 15% to 5% with treatment A instead of treatment B'. This gives already a better impression on the clinical relevance. However, the real clinical relevance of structural damage can only be based on cohort studies.

Because of the trend of lower progression rates over the years, we have proposed the structural integrity margin [11]. This concept assumes that a new treatment should show zero progression, while allowing some variation around zero due to measurement error. This so called structural integrity margin should be based on progression scores found in historic trials with licensed bDMARDs that have obtained a structural claim. This would imply a within group comparison as an alternative to superiority against placebo. If the mean progression score including the 95% confidence interval is entirely below the structural integrity margin, maintenance of structural integrity can be declared.

Given the limited progression observed in many trials, the question raises if it is still useful to use radiographs as an outcome in clinical trials. There are several arguments pro using radiographs. First, while the overall trend of radiographic progression is a decreasing one, still in recent trials observed radiographic progression was sufficient to discriminate between groups and formally prove inhibition of radiographic progression. This was both in trials using MTX plus placebo in MTX-inadequate responders or MTX in MTX-naïve patients as a control group [12]. The prevailing requirement for showing inhibition of progression is sufficient progression in the control arm. Appropriate trials include patients with a high risk of radiographic progression, based on (for instance) presence of aCCP or rheumatoid factor, baseline damage and elevated CRP. While trials formally prove overall inhibition, most inhibition is usually observed in the subgroups with relatively high baseline radiographic damage present. The usefulness of these predictors for radiographic progression has been recently shown in post-hoc analyses of the ORAL-SCAN trial with tofacitinib [13]. Moreover, there are populations such as the Japanese, which constitutively show a high level of progression [14]. Consequently, the selection of the correct study population is essential. Second, the EMA has proposed radiographs as a 'safety measure' in their draft guidance document for RA [15]. They differentiate between using radiographs as an outcome - to show inhibition of progression and to have this in the label - and using radiographs to document that there is no important deterioration. For the latter, they propose structural damage of hands and feet to be measured routinely by radiographs in the pivotal long-term trials, as a safety check to reassure that structural damage does not deteriorate during treatment, e.g. compared to an active comparator. A formal non-inferiority test is not required.

Are there alternative imaging measures? Not really at this point in time. The EMA accepts MRI as an additional, supportive imaging method, but not as a replacement for radiographs [15]. MRI has shown predictive validity in predicting progression of structural progression on radiographs over 24 weeks by MRI over 12 weeks, as well as 52-week progression on radiographs by 24-week progression on MRI [16]. However, MRI in RA is more difficult to standardise, and time-consuming, which makes it less feasible. As a consequence, MRI can only be performed according to appropriate regulatory standards in centres of excellence in the field of MRI, which consequently impedes feasibility of trial conduct and generalisability of results. Along similar lines, ultrasonography, while very popular in rheumatology, will not easily become a surrogate for assessing structural progression. The technique is highly operator-dependent, time consuming and unfeasible in trials, and a unified and broadly accepted scoring system is lacking. All other imaging techniques that potentially can be used to monitor structural progression in RA are -from a regular point of view- highly experimental, and several aspects of validity are currently lacking.

A method to increase the sensitivity of structural damage assessed on radiographs could be to change the reading process. Typically, two readers score all radiographs independently, blinded to patient identity, treatment group and time order. The average score of the two readers is used as the primary endpoint. Two changes could be implemented to increase sensitivity as well as increase precision: unblind the time order (increases sensitivity) and use (the average score of) three readers (increasing precision) [17,18].

Conflicts of interest

Désirée van der Heijde received consulting fees AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, UCB and is Director of Imaging Rheumatology BV.

Robert Landewé received consulting fees of AbbVie, Ablynx, Amgen, Astra-Zeneca, Bristol Myers Squibb, Celgene, Eli-Lilly, Janssen, Gilead, Galapagos, Glaxo-Smith-Kline, Novartis, Novo-Nordisk, Merck, Pfizer, Roche, Schering, TiGenix, UCB and is director of Rheumatology Consultancy BV.

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